toxicity, employed a defective animal model. Recently it has been shown that many of these animals have infections, but that in the absence of infection, iron does not induce liver fibrosis[32], leading to the conclusion that the infection of the animals not the use of the chelator under investigation, CP94, was responsible for the fibrosis, and this has been confirmed in a subsequent study using deferiprone in disease-free gerbils.[33]

In summary, due to scarcity of an appropriate animal model for predicting the human response to iron chelators, the results obtained in animal studies should be interpreted and have been interpreted herein with caution. The extensive clinical experience acquired during the long-term use of deferiprone by patients with thalassemia major greatly exceeds the value of the results observed in any short-term animal studies.

Clinical trials of deferiprone demonstrated that a dose of 75 mg/kg of body weight/day can control the progression of iron overload in patients with transfusion-dependant thalassemia.[8,25,27-29,31,35] The reduction or stabilization of the patients body iron load that is achieved with the use of deferiprone would be expected to contribute to some reduction on the incidence of cardiac disease, simply due to a decrease in the overall body iron load. This study has confirmed that conclusion, but the magnitude of protection was much greater than expected when measured against a chelator with equal or greater iron chelating ability, leading to the teaching presented in this study of an even greater protective effect than could be expected from overall iron reduction alone. The results also teach that the use of deferiprone has a beneficial impact on the prevention of cardiac disease among transfusion-dependant thalassemia patients.

Preferably the dosage form may be a sustained release formulation made in accordance with the common knowledge of a man skilled in the art and the constituents set out in Chart A below. By having a constant level of deferiprone in the body, we protect against the development of heart damage from fluctuating levels of non-transferrin-bound iron. Although the standard formulation provides protection, blood levels fall to very low levels after about 4 hours. Thus a sustained release formulation provides a greater level of protection by providing higher blood levels throughout the dosing period. Chart A illustrates one of the formulations prepared by the applicants as an example of a sustained release formulation of deferiprone, where the active ingredient is 500 mg. Other types of sustained release formulations are possible as well.

CHART A

DEFERIPRONE (L1) TABS AS 500 MG CORE

Ingredient Name	Mg Per Tablet
Hydroxypropyl Cellulose NF	6.0
Hydroxypropyl Methylcellulose USP	1.5
Polyethylene Glycol 8000 NF	4.5
Titanium Dioxide USP	6.0
Purified Water USP	132.0
Sub-Total	150.0
Cores:	
Deferiprone (L1) Tabs as 500 mg Core	600.0
Total (Excluding Water)	618.0

The Assignee completed other studies wherein the largest prospective clinical study ever conducted for an iron chelator was made. One hundred eighty-seven subjects with thalassemia were enrolled in this trial conducted by Drs. A. Cohen, R. Galanello, A. Piga, and V. De Sanctis in 3 centres in Italy and 1 center in the USA. Similar to what was observed in the patients discussed above in this disclosure, no heart failure occurred in any of the other study centres in patients participating in that study, treated with deferiprone for up to 5 years.

As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

TABLE 4

Demographic, chelation, and iron overload in patients with a worsening of cardiac function during the study period.

Patient Identification No.	Chelation therapy during study period	Age at start of the study	Age at start of chelation therapy with deferoxamine	Compliance with chelation therapy	% Ferritin >2500 ng/mL during the 2 years prior the study	% Ferritin >2500 ng/mL during the study period	HIC prior to study (SQUID*/Biopsy†)	Last HIC at study (SQUID*/Biopsy†)
48	Deferiprone	21	6	80	0	83	0.6/3.8	2.0/NA
96	Deferiprone	17	4	98	25	37	1.9/5.6	2.3/NA
14	Deferoxamine	26	12	86	75	37	NA/NA	1.1/NA
20	Deferoxamine	24	9	89	100	92	NA/NA	4.4/NA
40	Deferoxamine	22	7	96	0	77	0.3/NA	NA/NA
50§	Deferoxamine	20	6	92	0	0	NA/NA	0.5/NA
61	Deferoxamine	19	5	88	0	0	1.4/NA	1.6/NA
63	Deferoxamine	19	4	94	0	3	1.5/NA	1.4/NA
76	Deferoxamine	18	4	54	14	77	NA/NA	2.9/NA
77	Deferoxamine	18	4	93	0	3	NA/NA	1.4/NA
101	Deferoxamine	17	3	99	0	3	NA/NA	1.4/NA
122	Deferoxamine	13	6	95	0	0	1.1/NA	1.0/NA

*mg Fe/g liver wet weight

†mg FE/g liver dry weight

§Cardiac disease diagnosed at the first assessment worsened during study period